

## Results of HIV-infection model stabilization

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**Abstract:** In the paper considers a problem of stabilizing a HIV infection dynamics mathematical model that described by a system of differential equations with delay. A stabilizing control is constructed basing on the method of explicit solutions of Generalized Riccati Equations of the theory of analytical constructing regulator for systems of functional differential equations. For construct a feedback control we use the third variant of explicit solutions of the generalized Riccati equations. First and second variants of stabilization discussed in other authors articles. Considered stabilizing control for the system of differential equations with delay leads HIV-infection system to the small non-zero level of infection. Results of the research can be applied to analysis of some aspects of HIV dynamics.

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### 1. INTRODUCTION

In this paper we continue to consider the problem of constructing the feedback control, stabilizing the HIV model, the mathematical model described by a system of linear functional differential equations that allows to apply for the construction of control theory analytical construction of regulators for systems with (Kwon, 2010; Krasovskiy, 1962; Kim, 1998). In Kwon (2010) and Kim (1998) based on the explicit solution of the generalized Riccati equation obtained several options for feedback control for linear systems with delays. This approach is used to study the problem of stabilization of the considered model of HIV. In this part of the paper examines stabilizability HIV infection model, built on the basis of a third variant of explicit solutions GRE. In the first and second parts of the research applied control, built on the basis of a first and second variants of explicit solutions GRE. Computer simulations showed that all control stabilize consider HIV model, but stabilization characteristics are different.

#### 1.1 HIV-infection mathematical model

Classical mathematical model HIV-infection spread in the human body is a system of differential equations with delay (Bocharov, 2012; Ciupe, 2006):

$$\begin{cases} \dot{T}(t) = s - dT - kVT, \\ \dot{T}^*(t) = kVT - \delta T^* - d_x ET^*, \\ \dot{V}(t) = N\delta T^* - cV, \\ \dot{E}(t) = pT^*(t - \tau) - d_E E, \end{cases}$$

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where  $T(t)$  - number of uninfected T-cells,

$T^*(t)$  - number of infected T-cells,

$V(t)$  - number of free viral cells,

$E(t)$  - immune response, the number of effector cells generating by human body after drug stimulation,

$s$  - source of healthy cells,

$d$  - healthy cells mortality,

$p$  - effector cells activation rate,

$k$  - the rate of infection,

$b$  - infected cells mortality,

$d_x$  - immune response effectiveness,

$N$  - number of virus particles obtained from one infected cell,

$c$  - viral cells clearance,

$d_E$  - effector cell mortality,

$\tau$  - (delay) - time required effector cell for infection recognition,

$U$  - drug immune response stimulation that help human body generate effector cells and kill free viral cells in human blood.

The process regulation can be carried out at the expense of drug enhancing the immune response: in this case  $U$  is a control parameter of  $u(t)$ .

The parameters of the system (1) are presented in (Ciupe, 2006)

$$\begin{aligned} T(0) &= T_0, T^*(\varphi) = 0, V(0) = V_0, E(0) = 0, \varphi \in [-\tau, 0], \\ T_0 &= 10, T^*_0 = 0, V_0 = 10^{-9}, E_0 = 0.1, \\ s &= 0.103, d = 0.01025, p = 1.473, c = 0.557, \\ k &= 0.0000065, b = 0.514, d_x = 0.812, N = 2500, \\ d_E &= 0.618, \tau = 16.05, \\ \bar{V} &= -376.6967, \bar{T}^* = -0.1633, \bar{E} = -0.3892, \bar{T} = 13.2026 \end{aligned}$$

System (1) can be conveniently represented in matrix form as (Ciupe, 2006)

$$\dot{x}(t) = Ax(t) + A_\tau x(t - \tau) + Bu(t), \quad (2)$$

$$A = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -2 & 0 & 1 \\ 0 & 1285 & -6 & 0 \\ 0 & 0 & 0 & -6 \end{bmatrix},$$

$$A_\tau = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 1.473 & 0 & 0 \end{bmatrix},$$

$$B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}.$$

The system (2) has a root with a positive real part (Ciupe, 2006) and is unstable (El'sgol'ts, 1971). The considered task is to construct a feedback control

$$u[t, x(t), x(t+s)] = Cx(t) + \int_{-\tau}^0 E(s)x(t+s)ds, \quad (3)$$

stabilizing system (3). As mentioned above is not always HIV-infected cells may be derived from the human body, however, in contrast to the technical concept of the stabilization, when the solution tends to zero, we understand the following stabilization.

Control (3)  $\beta$ -stabilizes ( $\beta \in R^n$ ) system (2), if system (2) is  $\beta$ -asymptotically stable, i.e. every decision of this closed system tends to  $\beta$ .

## 1.2 The purpose and methodology of research

The purpose of this paper is to simulate the process of HIV replication in the human body and research the properties of

stabilizing feedback control, that was built on the basis of a first variant of explicit solutions GRE.

In Krasovski (1962), Kim (1996, 1998, 2004, 2011) and Kwon (2010) discuss how stabilizing control on the basis of generalized Riccati equation explicit solutions.

A third variant of explicit solutions GRE (Kwon, 2010) corresponds to the feedback control

$$u^*(x, y(\cdot)) = Cx + \int_{-\tau}^0 Dy(s)ds \quad (4)$$

and closed system

$$\dot{x}(t) = (A + BC)x(t) + A_\tau y(-\tau) + \int_{-\tau}^0 (BD + G(s))y(s)ds \quad (5)$$

This control is obtained by substituting (4) into the original system (2). There is

$$C = -N^{-1}B^T P,$$

$$D = -N^{-1}B^T P A_\tau,$$

$$R = A'_\tau P A_\tau.$$

In control (4), the  $4 \times 4$  matrix  $P$  is a solution of the matrix equation (Kim, 2004)

$$P(A + A_\tau) + (A' + A'_\tau)P + C_0 + \int_{-\tau}^0 \varphi_2(s) + C_3 = PKP, \quad (6)$$

where  $C_0$  and  $C_3$  - constant symmetric  $4 \times 4$  matrix,

$\varphi_2(\cdot)$  - symmetric  $4 \times 4$  matrix with continuous on  $[-\tau, 0]$  elements,

$$K = BN^{-1}B'.$$

To verify that the control (4)  $\beta$ -stabilizes system (2) is sufficient to show  $\beta$ -asymptotically stability of the closed system

$$\begin{aligned} \dot{x}(t) &= (A - BN^{-1}B'P)x(t) + A_\tau x(t - \tau) + \\ &+ \int_{-\tau}^0 (G(s) - BN^{-1}B'e^{-[PK-A'](\tau+s)} P A_\tau)x(t+s)ds. \end{aligned} \quad (7)$$

## 2. COMPUTER SIMULATION RESULTS

### 2.1 Solution of the matrix equation

Solution of equation (6) can be found analytically and equal

$$P_1 = \begin{bmatrix} 0 & 63 & 0 & 1 \\ 63 & 21514 & 60 & 382 \\ 0 & 60 & 0 & 1 \\ 1 & 382 & 1 & 10 \end{bmatrix}. \quad (8)$$

In this case  $\varphi_2(\cdot)$  is taken as a constant  $4 \times 4$  matrix all of whose elements are equal to 1, and  $C_0$  and  $C_3$  the selected constant  $4 \times 4$  matrices all of whose elements are equal to 64.9.

In this case, the term of the equation (7)

$$C_0 + \int_{-\tau}^0 \varphi_2(s) + C_3$$

becomes a constant  $4 \times 4$  matrix all of whose elements are equal to 1.

## 2.2 System trajectory construction

The trajectory of the system (4) (see Figure 1) converges to  $\beta$ , and hence control (4) is  $\beta$ -stabilizes.

When  $\tau = 16.05$  the system (5) tends to

$$\beta = \begin{bmatrix} 1.4507 \\ -0.0006 \\ -1.3396 \\ 0.0268 \end{bmatrix}.$$

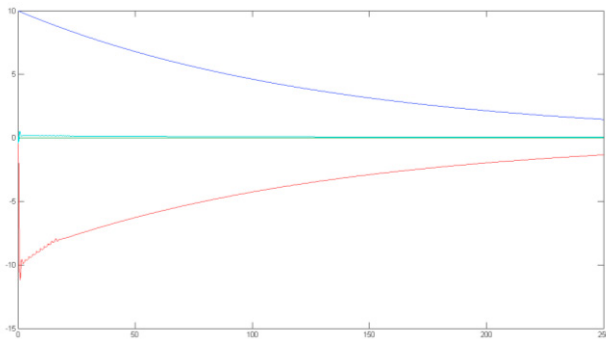


Fig. 1. The trajectory of the system (5).

Using the control (4) for stabilizing the system (5) can be observed a significant (to a negative value) reduction count of free viral cells in the human body ( $V(t)$  parameter in the (1) system of functional differential equations) and the number of infected T-cell ( $T^*(t)$  parameter in the (1) system of functional differential equations).

Control leads system (5) to a steady state with low viral load and a small amount of infected T-cells and can to stabilize system (5) in state with negative values of these parameters. These factors can be attributed to the positive results of application control, built on the third variant explicit solutions of generalized Riccati equation.

The negative consequences using control (4) for stabilizing the system (5) is reducing the number of effectors and uninfected T-cells ( $E(t)$  and  $T(t)$  parameters in the system of functional differential equations).

This inevitably occurs reduction in the immune functions of the human organism as a whole. With long-term using of stabilization may occur development immunopathological processes that ultimately can lead to autoimmune diseases and hypersensitivity to various infections.

In order to reduce the negative impacts of the considered control is proposed to apply it is not continuous, but discrete. Period of application of immune drugs offered alternate with recover periods.

This approach will significantly increase the amount of time needed to lead the system to a steady state, but will reduce the negative effects of therapy.

## 3. CONCLUSION

Thus, the feedback control is constructed on the basis of a first variant of generalized Riccati equation explicit solutions is  $\beta$ -stabilizes the spread of HIV-infection in humans.

At the same control characteristics tend to some non-zero value. That is, the control maintained replication of HIV-infection in the human body in a certain steady state.

This steady state is characterized by low level of infected T-cells and viral loads, but also human body immune function is in depressed state.

To reduce the negative impact of therapy on the human body are encouraged to apply discrete control, although this approach will increase the total time to lead the system in a steady state.

Comparing our results with the results of other authors Ciupe (2006), Jang (2011), Kwong (2011), Arts (2012), it should be noted that the considered control, built on the basis of a first variant of generalized Riccati equations explicit solutions not only leads the (1) system of functional differential equations describing the HIV-infection model dynamics in the human body, in a steady state with low viral load and allows to achieve remission of the disease at a level not dangerous to human life, but also can contribute to the complete disappearance of free viral cells and infected T-cells.

Remains an open the question about stabilizing properties of controls, built on the basis of the second and third variant of explicit solutions of generalized Riccati equations.

Subsequent articles will be considered building a stabilizing control on the basis of the remaining variants of explicit solutions GRE and discuss the results of their using for stabilizing the HIV-infection dynamics model that was built in the current article.

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